proteins for their tasks is achieved by the continuous action of natural selection—the driving force in evolution. Since in the cells of living organisms all functions are carried out by proteins, it is on proteins that natural selection operates at the molecular level. Those organisms with better proteins will tend to prosper, that is, to have more descendants. Hence the great variety of the molecular structure of proteins is the result of selection of proteins for more efficient chemical function. This variety makes the task of the protein chemist exceedingly hard. If molecular biology had had to await the one-by-one unraveling of the structure of proteins it might have taken a hundred years to learn what we now know.

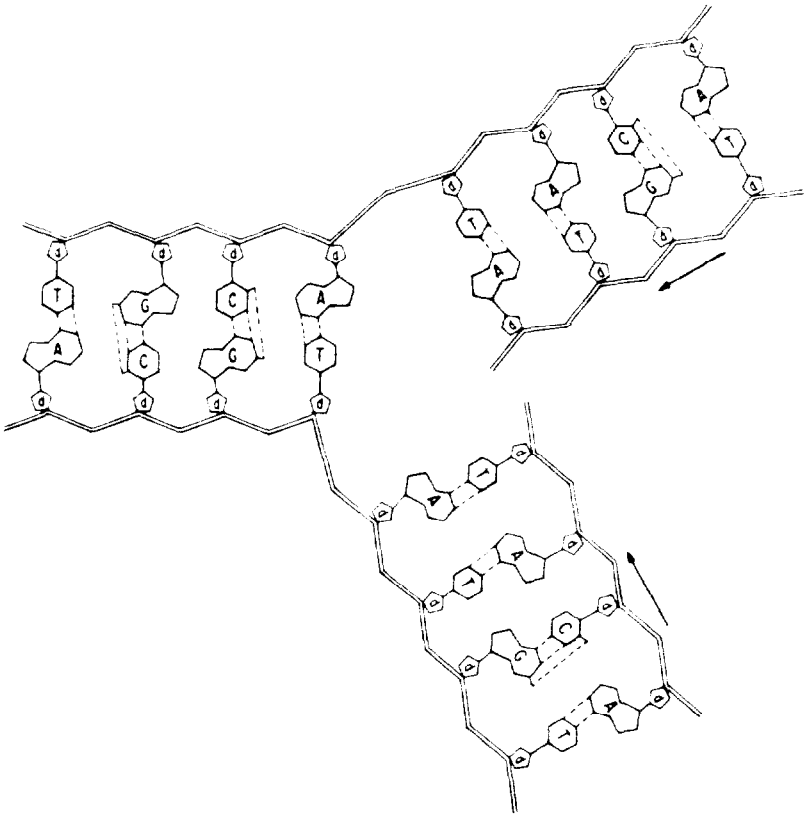
Fortunately, not all biological molecules are as idiosyncratic as proteins. In fact, the most important one, the DNA molecule, turned out to have a good sensible structure, very uniform as well as informative. The history of the identification of DNA with the genetic material of cells has been frequently told. Like the stock of an oil company with rich but still untapped resources, the rating of DNA in the marketplace of biological research fluctuated widely for many years. Most geneticists were inclined to believe DNA was the stuff that genes were made of: it was present in the cell nucleus where genes are kept, and its amount was reasonably constant from cell to cell in a given organism, as it should be if it represented the genetic material. Some biochemists were more skeptical; their analysis indicated that DNA was "too simple" in composition, made up of only four units or building blocks (nucleotides), which were called A, G, C, T from their initials. How could four units provide variety enough for the thousands of genes in a cell?

It was a bacteriologist, Oswald Avery, himself a biochemist turned geneticist by the force of his own findings, who delivered what ultimately proved to be the decisive blow for DNA. Avery was a short, bald, and benign gentleman with mischievously twinkling eyes. When his work led him to the study of DNA he was already illustrious for his contributions to the biology of the pneumonia bacillus. I first met him in 1943, when he had for years been studying a phenomenon discovered earlier by the British bacteri-

ologist Fred Griffith: an extract from a normal strain of pneumococcus, as the pneumonia bacillus is called, added to cells of a mutant strain could "transform" them to the normal form again. Most exciting, if extracts of several different strains were tested, each transformed the mutant into its own image; that is, the transforming agent or principle, whatever it was, was specific. It looked, at least to Avery's prepared mind, as if in each extract there were genes of the normal bacteria from which it had been taken, and such genes could enter the mutant bacteria and transform them. Avery believed it was so; he whispered it might be so, cautiously but with delighted excitement. He and his co-workers were seeking to identify the active principle in the extract. The more they purified it the more DNA it contained and the less of anything else. To make a long story short, DNA seemed to be it.

I won't go into the question, already belabored by historians of science, of why Avery's discovery did not immediately convince everyone. I myself, an early believer, was guilty some years later of a rash suggestion that bacteriophage genetic material was in the protein component, a scientific gaffe that sometimes still gives me a pang of shame like the memory of some rude or gauche behavior. Almost immediately, however, Hershey came to the rescue of DNA (and of me). In a set of experiments justly celebrated for their elegant simplicity, he and his colleague Martha Chase demonstrated that when a bacteriophage particle, which is composed of protein and DNA, attacks a bacterium, the protein is left outside and the DNA enters the bacterium, multiplies, and gives rise to more phage. In bacteriophage, as in Avery's bacteria, as in every living organism, we now are certain that the genes are DNA. (Some viruses manage with genes made of another kind of nucleic acid called RNA.)

The importance of the discoveries that identified as DNA the genetic material of bacteria first, then of phage, and ultimately of all organisms was that they make the problem of the gene into a straightforward problem of chemistry (while still remaining fully a problem of genetics). The structure of DNA at the molecular level was not yet known, but at least chemists and geneticists



A segment of DNA (drawn as in Figure E) undergoing replication. Each DNA chain serves as a template for lining up the appropriate units, which are then joined together into chains by specific catalysts. The arrows show the direction in which the new chains are growing as the "growing fork" moves to the left.

clarified the structure of DNA, our view of genes changed, from beads on a string to stretches of a chemical ribbon. Genes were stretches of DNA double helix. This knowledge raised new problems: How are the individual genes marked off in DNA? Where does each gene start and end?

One needed a different kind of tool to dissect DNA into genes; that tool proved to be genetic analysis of bacteria. The DNA of a bacterium is a single, naked DNA molecule, so long that if it were stretched out instead of being coiled in the bacterial cell it would

be a thousand times longer than the cell itself. In an analogy suggested by Seymour Benzer, a bacterium is like one of those lacquer boxes full of long noodles served in Chinese restaurants; in the bacterium the noodles are DNA. Soon after I had got bacterial genetics going with fluctuation-test experiments, two American geneticists, Edward Tatum and Joshua Lederberg, discovered that some bacteria can mate; they pair together so that genetic material can pass from one to the other. When the two bacteria in a mating pair differ by several hereditary characters, out of the mating there emerge some descendants that are hybrids, that is, having new combinations of characteristics derived from the two parents.

Soon a Franco-British team, working out of Paris and London, showed that when a bacterial mating pair is formed a stretch of DNA actually passes from one member of the pair—the donor—to the other—the recipient—like a thread passing through the eye of a needle. This DNA thread carries genes in a precise order. By stopping the process at various times, one can determine which genes enter first, which next, and so on. In this way geneticists can establish the order of genes in the bacterial DNA. For the bacterium *Escherichia coli*, the workhorse of geneticists, we now know the relative positions of about one thousand genes, probably one third or so of the total gene patrimony of that organism!

The most important event is what follows when a piece of DNA, with one or more genes, enters from a donor cell to a recipient cell. These genes line up very precisely with the corresponding genes already present in the cell; then one or more exchanges happen, so that a stretch of DNA from the donor, containing one or more genes, or even only a piece of a gene, comes to replace the corresponding piece of DNA in the recipient. This process, called *recombination*, is the key to the reshuffling of genetic material. Recombination takes place not only between genes, which are stretches of hundreds or thousands of units in DNA, but even between two adjacent units. Such reshuffling is not unique to bacteria. It occurs, for example, among genes in chromosomes of plants or animals whenever sex cells are pro-